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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

abobotulinumtoxinA (Dysport Therapeutic)

(Ipsen Biopharmaceuticals Canada, Inc.)

Indication: To reduce the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults

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Abbreviations

aboBoNTA	abobotulinumtoxinA (Dysport Therapeutic)
AE	adverse effect
CD	cervical dystonia
CDR	CADTH Common Drug Review
incoBoNTA	incobotulinumtoxinA (Xeomin)
ITC	indirect treatment comparison
ODB	Ontario Drug Benefit
onaBoNTA	onabotulinumtoxinA (Botox)

Drug	AbobotulinumtoxinA (Dysport Therapeutic)
Indication	To reduce the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults
Listing Request	As per indication
Manufacturer	Ipsen Biopharmaceuticals Canada, Inc.

Summary

Background

AbobotulinumtoxinA (aboBoNTA, Dysport Therapeutic) is a botulinum neurotoxin subtype indicated to reduce the subjective symptoms and objective signs of cervical dystonia (CD, spasmodic torticollis) in adults, and is available in single-use vials of 300 U and 500 U at submitted prices of $428.40 and $714.00, respectively. The recommended initial dose of aboBoNTA is 500 U intramuscularly as a divided dose among affected muscles in patients with and without a prior history of treatment with botulinum toxin. Re-treatment of 250 U to 1,000 U divided among affected muscles is recommended when the effect of a previous injection has diminished, but no sooner than 12 weeks after the previous injection.[1] The manufacturer is requesting that aboBoNTA be reimbursed in line with its indication.

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost comparison, presented as a budget impact analysis, estimating total drug costs based on claims for onabotulinumtoxinA (onaBoNTA) and incobotulinumtoxinA (incoBoNTA) from April 2015 to March 2016.[2] Claims from Ontario Drug Benefit (ODB) were obtained based on Limited Use Code 130 ("to reduce the subjective symptoms and objective signs of CD (spasmodic torticollis) in adults"). Clinical similarity was assumed on the basis of four head-to-head trials comparing initial doses of aboBoNTA to onaBoNTA,[3-6] as well as on the basis of an unpublished indirect treatment comparison (ITC) adding incoBoNTA as a comparator.[1] Costs were obtained from ODB list prices and the manufacturer;[7] partially used vials were assumed to be wasted. All other costs, such as administration and monitoring, were assumed equal. The manufacturer considered a scenario where all claims reimbursed for the comparators (onaBoNTA and incoBoNTA) were replaced by aboBoNTA. Determination of dose per claim for aboBoNTA was in line with a 3:1 or lower ratio as observed in clinical trials,[3-6] with some alteration to minimize wastage of aboBoNTA (Table 3). The manufacturer estimated the total cost reimbursed by ODB from April 2015 through March 2016 for onaBoNTA and incoBoNTA for CD to be $4.64 million. If claims had been reimbursed for aboBoNTA instead, the total cost reimbursed by ODB would have been $4.47 million, leading to an estimated savings of approximately $174,000 for patients with CD receiving botulinum toxin through ODB for that year.

Key Limitations

Uncertainty in assumption of clinical similarity: The ITC submitted by the manufacturer[2] reported a lack of statistically significant differences on the Toronto Western Spasmodic Torticollis Rating Scale severity or pain subscales, as well as in terms of adverse events (AEs) or dysphagia. Despite a comprehensive search, good statistical analyses, and results that were similar to those in a published ITC (which only reported comparators versus placebo); the lack of a systematic review approach toward the retrieved literature makes the results of the analysis uncertain. Additionally, statistically significant differences should be interpreted with caution in small networks with no calculation of power analysis (see CADTH Common Drug Review [CDR] Clinical Report, Appendix 8). The four head-to-head randomized controlled trials (RCTs) comparing aboBoNTA with onaBoNTA used a variety of dose ratios, with increased efficacy but also increased AEs (at 4:1)[5] and with inconsistent results in terms of statistical differences (at 3:1).[5,6] Only one trial concluded non-inferiority at a 2.5:1 ratio.[3] There was potential confounding with concomitant medication and carry-over effects and little assessment of equivalency or non-inferiority; none of the studies conducted multiplicity tests to control type I error in secondary outcomes. As such, the assumption of clinical similarity is uncertain. Additionally, nearly all patients in the head-to-head trials comparing aboBoNTA with onaBoNTA had previously been treated with and were stable on onaBoNTA; these are unlikely to be those who would primarily receive aboBoNTA in clinical practice in Canada. The clinical expert consulted by CDR indicated that patients who are responding to one botulinum toxin would not be switched to another. It is namely those naive to botulinum toxin or those who had failed to adequately respond to one of the comparators who would receive aboBoNTA; thus, it is uncertain if the trial results can be transferred to this population.

Inappropriate analysis type: The manufacturer conducted a budget impact analysis rather than a cost comparison, considering a scenario where 100% of claims for botulinum toxin for the treatment of CD are replaced by aboBoNTA. The analysis inflates the manufacturer's conclusion of cost savings. Additionally, as the number of beneficiaries has not been provided, and it is not possible to derive the number of beneficiaries from the data set, it is difficult to generalize the results to other jurisdictions or to individual patients. CDR used the mean doses and standard deviations from the head-to-head trials, and the means and standard deviations of the provided claims data, to model distributions for a probabilistic analysis to estimate relative costs per patient.

Inappropriate dosing conversion: The manufacturer's use of claims data was helpful in establishing the substantial variation in the dose for botulinum toxins for CD in clinical practice relative to that expected based on monograph-recommended doses. The assumption that claims for aboBoNTA would be limited to the maximum recommended dose while comparators are reimbursed at doses far beyond those outlined in their respective product monographs: a) is unlikely to reflect clinical practice, given what is observed in the claims data; b) undermines the dose-equivalency ratios on which the assumption of clinical similarity is based; and c) artificially lowers the relative cost of aboBoNTA. CDR's probabilistic analysis assumed the ratio of 2.5:1 (for aboBoNTA to onaBoNTA or incoBoNTA) cited in the manufacturer's submission as the most appropriate (and most widely cited) ratio[2] for all analyses where duration of action was assumed to be similar.

Inappropriately conducted extended duration scenario: A statistically significant difference in duration of effect was observed in an RCT when aboBoNTA was dosed at a 4:1 ratio compared with onaBoNTA, and an increased but non-statistically significant extended duration was observed at a 3:1 ratio.[5] The manufacturer interpreted this to imply a duration of effect of 16 weeks whenever a claim conversion led to aboBoNTA being dosed at a 4:1 ratio, and a duration of effect of 13 weeks when aboBoNTA was dosed at a 3:1 ratio, and concluded that the substitution of aboBoNTA would result in further savings under these assumptions. However, the manufacturer's dose conversion table results in only the lowest doses of aboBoNTA having an assumed extended effect (i.e., those under 300 U have a duration of 13 weeks to 16 weeks, while those above 300 U have a duration of only 12 weeks, as is assumed for the comparators), which is unlikely to reflect clinical reality. CDR conducted a probabilistic analysis assuming a ratio of 4:1, with aboBoNTA having a duration of effect of 16 weeks compared with a duration of effect of 12 weeks for onaBoNTA. CDR also incorporated the cost of botulinum toxin administration and neurology consults, as these costs would differ between comparators with differing durations of action. The possibility of increased AEs with higher ratios[5] of aboBoNTA was not incorporated into CDR's analysis, but would further increase costs relative to onaBoNTA.

Issues for Consideration

Potential extended duration may be preferred by patients: While the data supporting a longer duration of effect for aboBoNTA are limited,[4,5] and do not suggest cost savings given the manufacturer's proposed dosing ratios (see CDR's extended duration scenario analysis), should the duration of effect be extended without increased AEs, this may be preferred by patients as potentially more convenient, time-saving, and less painful.

Per-unit costing: The submitted price of aboBoNTA per unit is equivalent to that of onaBoNTA when a 2.5:1 ratio is assumed. If vial sizes for aboBoNTA were available to account for this dose ratio (i.e., if aboBoNTA came in 125 U, 250 U, and 500 U sizes to match the available 50 U, 100 U, and 200 U onaBoNTA vials), the cost of treatment with both drugs would be identical, if dosed at a 2.5:1 ratio. As only 300 U and 500 U vial single-use sizes of aboBoNTA are available, this increased wastage of excess medication is the main driver of the additional cost for aboBoNTA when compared with onaBoNTA (see all CDR reanalyses). This effect may be mitigated in clinical practice if clinicians alter dosing to minimize vial wastage, but is unlikely to be eliminated. The per-dose equivalent unit cost of aboBoNTA is 8% more than that of incoBoNTA at a 2:5 to 1 ratio (500 U is $714 for aboBoNTA compared with 200 U at $660 for incoBoNTA; see Table 1), thus, both the higher price per equivalent unit and the increased wastage of medication drive the increased cost of aboBoNTA.

Results / Conclusions

While the manufacturer's results suggest that aboBoNTA would be cost-saving in comparison with a combination of onaBoNTA and aboBoNTA at the 2015 to 2016 market share reimbursed by ODB, reanalyses by CDR found that, assuming a 2.5:1 dosing ratio of aboBoNTA to comparators, and a 12-week duration of effect, aboBoNTA maintenance therapy ($4,641 per patient per year, 95% range: $1,856 to $9,901) was, on average, $189 more expensive than that of onaBoNTA ($4,452 per patient per year, 95% range: $1,547 to $10,056) based on observed use of onaBoNTA from claims data. Similarly, when compared with incoBoNTA, aboBoNTA maintenance therapy ($4,492 per patient per year, 95% range: $1,856 to $11,757) was, on average, $502 more than therapy with incoBoNTA ($3,990, 95% range: $1,430 to $10,725), based on observed use of incoBoNTA from claims data. An analysis considering only dose distributions used in head-to-head clinical trials comparing aboBoNTA and onaBoNTA yielded similar results. Under these assumptions, the cost per unit of aboBoNTA would need to be reduced by 3.3% to be cost-neutral to onaBoNTA and by 11.2% to be cost-neutral to incoBoNTA.

AboBoNTA is priced to be equivalent to the cost of onaBoNTA when a 2.5:1 dosing ratio is assumed, but is 8% more expensive than incoBoNTA per dose-equivalent unit. The absence of a vial size equivalent to the smallest available size of onaBoNTA and incoBoNTA may result in increased wastage of medication.

Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

Table 1: Cost Comparison Table for Botulinum Toxin A for Cervical Dystonia

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Cost per Treatment ($)[a]	Average Annual[b] Drug Cost ($)[a]
AbobotulinumtoxinA (Dysport Therapeutic)	300 U 500 U	Vial for injection	428.4000[c] 714.0000[c]	Initially 500 U IM divided among affected muscles. Re-treatment doses ranged from 250 to 1,000 U in clinical trials. Re-treatment should not occur in intervals of less than 12 weeks.	Initial: 714 Re-treatment: 428 to 1,428	2,428 to 6,426
IncobotulinumtoxinA (Xeomin)	50 U 100 U	Vial for injection	165.0000 330.0000	The usual total dose does not exceed 200 U IM divided among affected muscles, but up to 300 U may be given. The period between re-treatments is recommended to be at least 12 weeks.	Typically up to 660, may be up to 990	Typically up to 3,300; may be up to 4,950
OnabotulinumtoxinA (Botox)	50 U 100 U 200 U	Vial for injection	178.5000 357.0000 714.0000	Trial doses ranged from 140 U to 280 U IM divided among affected muscles; in clinical practice, doses from 200 U to 360 U have been used effectively. Repeat doses should be administered when clinical effect diminishes, but not more than every 2 months. Maximum cumulative dose should not exceed 360 U in a 3-month period.	714 to 1,428[d]	3,570 to 7,140[d]

IM = intramuscularly.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed March 2017)[7] unless otherwise indicated, and do not include dispensing fees.

[a] Cost per treatment includes wastage of excess medication in vials.

[b] Annual drug cost assumes initial dose and subsequent treatments at weeks 12, 24, 36, and 48.

[c] Manufacturer's submitted price.

[d] Range of 200 U to 360 U every 12 weeks.

Appendix 1: Reviewer Work Sheets

Table 2: Summary of Manufacturer's Submission

Drug Product	**AbobotulinumtoxinA (Dysport Therapeutic)**
Treatment	AbobotulinumtoxinA
Comparator(s)	OnabotulinumtoxinA IncobotulinumtoxinA
Study Question	If all onaBoNTA and incoBoNTA claims reimbursed were instead reimbursed for aboBoNTA, what would be the additional cost or savings to a provincial drug plan?
Type of Economic Evaluation	Cost comparison presented as a budget impact analysis
Target Population	Adult patients diagnosed with CD (ST)
Perspective	Canadian public drug payer
Outcome Considered	Drug costs
Key Data Sources	
Cost	ODB formulary for comparators, manufacturer for aboBoNTA
Clinical Efficacy	Four head-to-head trials of aboBoNTA compared with onaBoNTA Unpublished indirect treatment comparison of aboBoNTA, incoBoNTA, and onaBoNTA
Harms	Four head-to-head trials of aboBoNTA compared with onaBoNTA. Unpublished indirect treatment comparison of aboBoNTA, incoBoNTA, and onaBoNTA
Utilization Data	Unpublished IMS Brogan Data Services data set on all onaBoNTA and incoBoNTA claims reimbursed by ODB between April 2015 and March 2016 under LU Code 130 for CD
Time Horizon	One year
Results for Base Case	The manufacturer concluded that if all claims for onaBoNTA or incoBoNTA reimbursed for CD by ODB between April 2015 and March 2016 had instead been reimbursed for an equivalent dose of aboBoNTA, ODB would have saved $173,836 over that year.

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); CD = cervical dystonia; incoBoNTA = incobotulinumtoxinA (Xeomin); LU = Limited Use; ODB = Ontario Drug Benefit; onaBoNTA = onabotulinumtoxinA (Botox); ST = spasmodic torticollis.

Manufacturer's Results

The manufacturer submitted a cost comparison presented as a budget impact analysis, and estimated total drug costs using IMS Brogan data for all claims reimbursed by ODB for onaBoNTA and incoBoNTA under Limited Use Code 130 ("to reduce the subjective symptoms and objective signs of cervical dystonia (CD, spasmodic torticollis) in adults") between April 2015 and March 2016.[8] Costs per vial were ODB list prices for comparators and provided by the manufacturer for aboBoNTA. All other costs, such as administration and monitoring, were assumed similar between comparators. The manufacturer then calculated costs for a hypothetical scenario in which *all claims* reimbursed for the comparators are instead reimbursed for aboBoNTA. Conversions from claims for comparators to aboBoNTA were done according to Table 3, based on the ratio of less than 3:1 demonstrated in clinical trials[3-6] and altered to minimize vial wastage; any claim for more than 3,000 U of onaBoNTA or incoBoNTA was excluded, although at this setting, no claims were excluded.

Table 3: Manufacturer's Assumed Dose Conversion for Base-Case Cost Comparison

onaBoNTA or incoBoNTA Dose Dispensed	# of aboBoNTA 300 U Vials Dispensed	# of aboBoNTA 500 U Vials Dispensed	Corresponding aboBoNTA Dose Dispensed	Approximate AboBoNTA Ratio (Dispensed not Necessarily Injected)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); incoBoNTA = incobotulinumtoxinA (Xeomin); onaBoNTA = onabotulinumtoxinA (Botox); U = units.

Source: Adapted from Table 5-4 in manufacturer's pharmacoeconomic submission.[2]

The manufacturer estimated the total cost reimbursed by ODB from April 2015 through March 2016 for onaBoNTA and incoBoNTA to be $4.64 million, and that equivalent claims reimbursed for aboBoNTA would have cost $4.47 million, leading to an estimated savings of approximately $174,000 for the reimbursement of botulinum toxin for CD by ODB for that year (Table 4).

Table 4: Manufacturer's Base-Case Analysis Results

Scenario	Total Drug Cost
Current Scenario (without aboBoNTA)	
onaBoNTA	$4,073,905.50
incoBoNTA	$570,570.00
Total [A]	$4,644,475.50
Hypothetical Scenario (with aboBoNTA)	
aboBoNTA [B]	$4,470,639.60
Incremental Cost [B – A]	–$173,835.90

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); incoBoNTA = incobotulinumtoxinA (Xeomin); onaBoNTA = onabotulinumtoxinA (Botox).

Source: Adapted from Table 5-5 in manufacturer's pharmacoeconomic submission.[2]

The manufacturer then conducted an "extended duration scenario analysis" in which, under the conversion rules outlined in Table 3, aboBoNTA doses at ratios above 3:1 but below 4:1 were assumed to have a duration of 13 weeks, while those above 4:1 were assumed to have a duration of 16 weeks, compared with a 12-week duration assumed for doses at ratios below 3:1, and for comparators. Under these assumptions, and without considering differences in administration costs or AEs, the manufacturer estimated that the use of aboBoNTA rather than onaBoNTA or incoBoNTA would save the ODB approximately $207,000 for the reimbursement of botulinum toxin between April 2015 and March 2016 (Table 5).

Table 5: Manufacturer's Extended Duration Scenario Results

Scenario	Total Drug Cost
Current Scenario (without aboBoNTA)	
onaBoNTA	$4,073,905.50
incoBoNTA	$570,570.00
Total [A]	$4,644,475.50
Hypothetical Scenario (with aboBoNTA)	
aboBoNTA [B]	$4,437,446.84
Incremental Cost [B – A]	–$207,028.66

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); incoBoNTA = incobotulinumtoxinA (Xeomin); onaBoNTA = onabotulinumtoxinA (Botox).

Source: Table 5-6 in manufacturer's pharmacoeconomic submission.[2]

CADTH Common Drug Review Results

Initial doses – probabilistic analysis based on trial-dose distributions

While the manufacturer's economic analysis was based entirely around ODB claims data, CADTH Common Drug Review (CDR) explored the costs of comparators if they were used in a manner similar to those of the head-to-head clinical trials used to inform the assumption of clinical similarity. CDR also wished to explore relative costs on a per-patient or per-claim (rather than per-population) basis.

In order to explore the uncertainty around cost per patient-dose, given the varying vial sizes and mean initial doses used in the clinical trials, an exploratory probabilistic analysis was undertaken by CDR to estimate the mean cost difference per starting dose between aboBoNTA and onaBoNTA. Mean dose and standard deviations from the four head-to-head trials[3-6] comparing aboBoNTA with onaBoNTA were mapped to a beta distribution to restrict the range of possible doses to the minimum and maximum used in the trials. The 10,000 hypothetical patients were assigned doses of both aboBoNTA and onaBoNTA from these distributions and, after converting draws from the beta distribution back to actual doses, the costs of those doses were calculated using the available vial sizes and assuming wastage of additional medication. Like the manufacturer, where multiple aboBoNTA to onaBoNTA dose ratios were available — such as where trials incorporated multiple groups of different ratios, but only reported the mean dose and standard deviation for one comparator — CDR used the most widely cited ratio of 2.5 to 1.[2]

The mean dose, mean cost, and mean incremental cost (savings) from 10,000 draws for each trial are reported in Table 6. The mean initial dose of aboBoNTA was an average of $29 to $179 more expensive per hypothetical dose than onaBoNTA using the dose distributions reported in the head-to-head trials.

Table 6: CDR-Modelled Mean Dose and Cost of aboBoNTA and onaBoNTA Using Dose Parameters From Head-to-Head Trials

	Doses Reported in Trial		Modelled Results (10,000 Draws)				
Trial	**aboBoNTA (U)**	**onaBoNTA (U)**	**Mean Dose (U) (SD) aboBoNTA**	**Mean Dose (U) (SD) onaBoNTA**	**Mean Cost aboBoNTA ($, 95% range)**	**Mean Cost onaBoNTA ($, 95% range)**	**Mean Additional Cost (Savings) With aboBoNTA**
Yun et al. 2015[3] Ratio = 2.5:1	Mean: 361.04 SD: 57.91 Min: 200 Max: 400	Mean:144.41 SD: 23.16 Min: 80 Max: 160	361 (58)	144 (23)	666.30 (428 to 714)	637.07 (357 to 714)	$29.24
Odergren et al. 1998[6] Ratio = 3:1	Mean: 477 SD: 131 Min: 240 Max: 720	Mean: 152 SD: 45 Min: 70 Max: 240	477 (131)	152 (45)	808.59 (428 to 1,142)	630.07 (357 to 892)	$178.52

	Doses Reported in Trial		Modelled Results (10,000 Draws)				
Trial	**aboBoNTA (U)**	**onaBoNTA (U)**	**Mean Dose (U) (SD) aboBoNTA**	**Mean Dose (U) (SD) onaBoNTA**	**Mean Cost aboBoNTA ($, 95% range)**	**Mean Cost onaBoNTA ($, 95% range)**	**Mean Additional Cost (Savings) With aboBoNTA**
Ranoux et al. 2002[5] Ratio = 3:1 or 4:1	NR, ratio of 2.5:1 modelled	Mean:104.44 SD: 20.30 Min: 70 Max: 180	262 (50)	105 (20)	492.83 (428 to 714)	457.08 (357 to 536)	$35.75
Rystedt et al. 2015[4] Ratio = 1.7:1, 3:1	Mean: 169 SD: 63 Min: 50 Max:400	NR, ratio of 2.5:1 modelled	167 (63)	67 (25)	436.60 (428 to 714)	378.08 (357 to 536)	$58.52

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); incoBoNTA = incobotulinumtoxinA (Xeomin); NR = not reported; SD = standard deviation; onaBoNTA = onabotulinumtoxinA (Botox.

Note: All ratios in the table are reported in the order aboBoNTA (U) : onaBoNTA (U).

Subsequent doses – monograph-recommended ranges

These trials only consisted of initial treatment with botulinum toxin for CD. The aboBoNTA product monograph[1] suggests that repeat doses of aboBoNTA be between 250 U and 1,000 U, divided among affected muscles. The product monograph for onaBoNTA[9] suggests that, in clinical practice, a range of 200 U to 360 U is used for CD, while the incoBoNTA product monograph[10] suggests that doses should not exceed 200 U to 300 U. Drug costs, including wastage of excess medication, for doses across the full range recommended for aboBoNTA re-treatment are presented in Table 7, assuming a dose ratio of 2.5 to 1 for aboBoNTA compared with both onaBoNTA and incoBoNTA. Whether aboBoNTA was more expensive or less expensive than onaBoNTA depended on the dose being prescribed, while aboBoNTA was almost always more expensive than incoBoNTA.

Table 7: Cost Per Dose of aboBoNTA Compared With onaBoNTA and incoBoNTA Across the Full Range of Recommended Maintenance Doses

aboBoNTA Dose (U)	onaBoNTA/ incoBoNTA Dose (U) (2.5:1)	aboBoNTA Cost per Dose ($)	onaBoNTA Cost per Dose ($)	Additional Cost (Savings) aboBoNTA vs. onaBoNTA ($)	incoBoNTA Cost per Dose ($)	Additional Cost (Savings) aboBoNTA vs. incoBoNTA ($)
250	100	428.40	357.00	71.40	330.00	98.40
300	120	428.40	535.50	(107.10)	495.00	(66.60)
350	140	714.00	535.50	178.50	495.00	219.00
400	160	714.00	714.00	0	660.00	54.00
450	180	714.00	714.00	0	660.00	54.00
500	200	714.00	714.00	0	660.00	54.00
550	220	856.80	892.50	(35.70)	825.00	31.80
600	240	856.80	892.50	(35.70)	825.00	31.80
650	260	1,142.40	1,071.00	71.40	990.00	152.40
700	280	1,142.40	1,071.00	71.40	990.00	152.40
750	300	1,142.40	1,071.00	71.40	990.00	152.40

aboBoNTA Dose (U)	onaBoNTA/ incoBoNTA Dose (U) (2.5:1)	aboBoNTA Cost per Dose ($)	onaBoNTA Cost per Dose ($)	Additional Cost (Savings) aboBoNTA vs. onaBoNTA ($)	incoBoNTA Cost per Dose ($)	Additional Cost (Savings) aboBoNTA vs. incoBoNTA ($)
800	320	1,142.40	1,249.50	(107.10)	1,155.00	(12.60)
850	340	1,428.00	1,249.50	178.50	1,155.00	273.00
900	360	1,428.00	1,428.00	0	1,320.00	108.00
950	380	1,428.00	1,428.00	0	1,320.00	108.00
1,000	400	1,428.00	1,428.00	0	1,320.00	108.00

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); incoBoNTA = incobotulinumtoxinA (Xeomin); onaBoNTA = onabotulinumtoxinA (Botox); U = units; vs. = versus.

Average claim – probabilistic analysis based on ODB claims data

The manufacturer used ODB data provided by IMS Brogan for all onaBoNTA and incoBoNTA claims reimbursed between April 2015 and March 2016 for CD (Limited Use Code 130), and assumed a hypothetical situation where all such claims were instead reimbursed for aboBoNTA.[8] In order to do so, the manufacturer assumed the units per claim conversion amounts outlined in Table 3. However, assuming that all claims above 400 U of the comparators (328 claims, the largest of which was for 1,200 U of onaBoNTA) would be dispensed as 1,000 U of aboBoNTA (i.e., the upper limit of the product-monograph-recommended dose) is unlikely to reflect whatever practice is driving the prescription and reimbursement of such high doses, undermines the equivalency ratios in the assumption of clinical similarity, and artificially lowers the relative cost of aboBoNTA.

Additionally, comparing the cost of a 100% market share of aboBoNTA with the 88% onaBoNTA market share and 12% incoBoNTA market share seen in the April 2015 through March 2016 ODB claims data assumes that this market share is both stable over time and across jurisdictions, which seems unlikely. The substitution of aboBoNTA for all incoBoNTA claims for this time period would have cost ODB $33,079 more than the $570,570 reimbursed for incoBoNTA; aboBoNTA is more expensive than incoBoNTA under all of the manufacturer's own assumptions.

When the manufacturer's model is adjusted so as to exclude all onaBoNTA or incoBoNTA claims above 500 U rather than 3,000 U, the resulting incremental cost of aboBoNTA is $29,581 *more* than that of the comparators for all remaining claims reimbursed by ODB between April 2015 and March 2016, versus $173,836 less, as reported in the manufacturer's base case. However, this method eliminates the most expensive claims available and still does not estimate cost on a per-claim or per-patient (rather than a per-population) basis.

To adjust for the bias incurred when comparators are assumed to be dispensed at doses substantially higher than their monograph ranges while aboBoNTA was not, as well as to estimate the mean additional costs or savings per claim rather than per population per year (while still incorporating all the available data), CDR conducted probabilistic analyses mapping the claims data to gamma distributions for onaBoNTA and incoBoNTA using the mean and standard deviation of claims reimbursed for each drug. These distributions were then used to make 10,000 random draws as described in the probabilistic analysis using trial-dose distributions; however, this time without restricting the ranges, as was done to better reflect trial data, as real-world claims data appear to vary substantially. Results for this analysis are outlined in Table 8. The mean cost of aboBoNTA ($1,071 per claim) was $44 more than onaBoNTA ($1,027 per claim) using onaBoNTA claims data; when incoBoNTA claims data were used, the mean cost of aboBoNTA ($1,037 per claim) was $116 more than that of incoBoNTA ($921 per claim). Assuming 4.3 claims per year (52/12 weeks), the average annual cost of aboBoNTA per patient is $189 more than for onaBoNTA (using onaBoNTA data) and $502 more than for incoBoNTA (using incoBoNTA data). The cost of aboBoNTA would need to be reduced by 11.2% to equal the cost of incoBoNTA, and reduced by 4.1% to be equal to the cost of onaBoNTA.

These results did not differ substantially when alternate analyses were conducted using ODB claims data from January 2013 through March 2016 (also provided by the manufacturer from IMS Brogan[8]). While not providing them to CDR for review, the manufacturer subsequently submitted adjusted analysis results where aboBoNTA substitute claims were not limited to

recommended doses and which concluded that the average cost of aboBoNTA ($987.66 per claim) would need to be reduced by 4.16% to be cost-neutral to onaBoNTA ($946.54 per claim) using onaBoNTA claims data, and where using incoBoNTA data resulted in the average cost of aboBoNTA ($974.65 per claim) needing to be reduced by 11.84% to be cost-neutral to that of incoBoNTA ($859.29). These results are similar to those of CDR's reanalyses.

Table 8: CADTH Common Drug Review–Modelled Mean Dose and Cost of aboBoNTA, onaBoNTA, and incoBoNTA Using ODB Claims Data

Parameter	onaBoNTA ODB claims data	incoBoNTA ODB claims data
ODB April 2015 to March 2016 utilization data parameters	N: 4,256 Mean: 263 U SD: 143 U	N: 601 Mean: 250 U SD: 183 U
10,000 draws from gamma distributions with above parameters	Mean: 264 U SD: 143 U Mean cost: $1,027.40 (95% range: $357 to $2,321)	Mean: 250 U SD: 184 U Mean cost: $ 920.76 (95% range: $330 to $2,475)
Same 10,000 draws if aboBoNTA reimbursed instead (ratio 2.5:1)	Mean: 661 U SD: 356 U Mean cost: $1,071.04 (95% range: $428 to $2,285)	Mean: 625 U SD: 460 U Mean cost: $ 1,036.69 (95% range: $428 to $2,713)
Mean additional cost (95% CI) per claim with aboBoNTA versus comparator	**$43.64**	**$115.92**
Costs per year assuming an average of 52/12 mean claims per year	aboBoNTA: $4,641.19 (95% range: $1,856 to $9,901) onaBoNTA: $4,452.07 (95% range: $1,547 to $10,056) **Difference (aboBoNTA – onaBoNTA): $189.11**	aboBoNTA: $4,492.30 (95% range: $1,856 to $11,757) incoBoNTA: $3,989.99 (95% range: $1,430 to $10,725) **Difference (aboBoNTA – incoBoNTA): $502.32**

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); CI= confidence interval; incoBoNTA = incobotulinumtoxinA (Xeomin); SD = standard deviation; ODB = Ontario Drug Benefit; onaBoNTA = onabotulinumtoxinA (Botox).

Extended duration scenario analysis – probabilistic analysis based on ODB claims data

There are signals[4,5] that at higher-dose ratios, aboBoNTA may have a longer duration of effect than onaBoNTA; these durations were estimated by the manufacturer as 13 weeks when a 3:1 ratio is used and 16 weeks when a 4:1 ratio is used.[2] However, as the manufacturer used the vial conversions outlined in Table 3 rather than assuming a predefined ratio for conversion, only the lowest doses of aboBoNTA have an assumed extended effect (i.e., those under 300 U have a duration of 13 weeks to 16 weeks, while those above 300 U only last 12 weeks), which is unlikely to reflect clinical reality. If aboBoNTA does indeed have an extended duration of action compared with onaBoNTA at a 3:1 or 4:1 ratio, then the average patient (not only those on the lowest doses) will experience a longer effect.

While there is insufficient information available to assess whether these signals will correspond to longer durations in clinical practice, CDR conducted a sensitivity analysis assuming that a 4:1 ratio of aboBoNTA to onaBoNTA corresponds to a 16-week duration of effect, compared with 12 weeks for onaBoNTA. While the higher-dose ratio increases the cost per dose of aboBoNTA, this is partially offset by requiring fewer doses per year (3.25 versus 4.33). Additionally, while administration and specialist appointment costs were considered equal in the analyses (assuming similar duration between comparators), should aboBoNTA have a 16-week duration of effect, its use would also accrue fewer of these costs (3.25 per year versus 4.33). When onaBoNTA is assumed to be dosed at 250 U every 12 weeks and aboBoNTA at 1,000 U every 16 weeks (doses within the recommended range of both product monographs), the annual cost of maintenance therapy (including administration) with aboBoNTA ($5,190 per patient) was $590 more than onaBoNTA ($4,600). If the mean dose of onaBoNTA (263 U every 12 weeks [Table 8]) modelled using ODB

utilization data is used and converted to 4:1 aboBoNTA every 16 weeks, then the annual cost of maintenance therapy and administration of aboBoNTA ($5,879 per patient) is $676 more than that of onaBoNTA ($5,203 per patient). These scenarios are detailed in Table 9.

Table 9: CADTH Common Drug Review Scenario Analysis of Extended Treatment Duration of aboBoNTA

	Dosing Within Product Monograph Range (4:1 Ratio)		Dosing/costs From Utilization Data Model (4:1 Ratio)	
	onaBoNTA dose 250 U every 12 weeks	aboBoNTA dose 1,000 U every 16 weeks	onaBoNTA mean dose 263 U every 12 weeks	aboBoNTA mean dose 1,052 U every 16 weeks
Mean drug cost per claim	$892	$1,428	$1,032 (95% range: $357 to $2,320)	$1,640 (95% range: $428 to $3,570)
Cost per injection appointment[11]	$169			
Annual drug cost	$3,868	$4,641	$4,471 (95% range: $1,547 to $10,055)	$5,330 (95% range: $1,392 to $11,602)
Annual appointment cost	$732	$549	$732	$549
Annual total cost	$4,600	$5,190	$5,203 (95% range: $2,279 to $10,788)	$5,879 (95% range: $1,941 to $12,152)
Additional cost (savings) with aboBoNTA	$590		$342	

aboBoNTA = abobotulinumtoxinA (Dysport Therapeutic); onaBoNTA = onabotulinumtoxinA (Botox).

Note: Appointment costs ($168.95 per visit and administration) were taken from the Ontario Schedule of Physician Services[11] and include: A113 (complex neuromuscular assessment): $89.85; G875 (first injection of botulinum toxin): $40; G876 (maximum number of billable additional injections [11]): $110; and G878 (electromyography guidance for determining injection site of two or more injections): $28.10. onaBoNTA every 12 weeks was assumed to accrue 4.33 doses and appointments over a year, while abobotulinumtoxinA every 16 weeks accrued 3.25. The maximum number of billable injections was assumed to apply maximum possible savings to aboBoNTA.

While the per-unit price of aboBoNTA is set to be equivalent to that of onaBoNTA if a 2.5 to 1 ratio is assumed, the absence of equivalently small vial sizes leads to more wastage of excess medication for aboBoNTA, especially at lower doses, which will increase costs to payers. It is likely that clinicians will use doses that minimize vial wastage to some extent (e.g., a patient who would receive 308 U of botulinum toxin in the model would likely receive 300 U in the real world); however, this adjustment will not always be possible. Additionally, the least expensive comparator at the manufacturer's assumed dose ratios is incoBoNTA; aboBoNTA (at 2.5:1 ratio) and onaBoNTA (at 1:1 ratio) are 8% more expensive per dose-unit than incoBoNTA.

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